9.0 EPIDEMIOLOGY OF ADULT BRAIN CANCER

STATEMENT TO THE PUBLIC

The reviewers expressed their judgments using two distinct sets of guidelines to evaluate the evidence:

- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for adult brain cancer, their classifications for EMFs was "possible human carcinogen" (IARC's Group 2B). Panels convened by IARC and the National Institutes for Environmental Health Sciences on the other hand thought the evidence was "inadequate" to make a classification (IARC's Group 3).***

- ***Using the Guidelines developed especially for the California EMF program, one of the reviewers was "prone to believe" that high residential EMFs cause some degree of increased risk of adult brain cancer, and the other two were "close to the dividing line between believing or not believing."***

There are several reasons for the differences between the DHS reviewers and those of IARC. The three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them. Adult brain cancer has an incidence of around 1/10,000 per year. If one doubled this rate to 2/10,000 per year and accumulated it over a lifetime of continuous high exposure one would accumulate a lifetime risk of 1%. Thus the vast majority (99%) of highly exposed people would still not contract this disease. Furthermore, calculations suggest that the fraction of all cases of adult brain cancer that one could attribute to EMFs would be no more than a few percent of the total cases (if any). Nevertheless, if EMFs do contribute to the cause of this condition, even the low fractions of attributable cases and the size of accumulated lifetime risk of highly exposed individuals could be of concern to regulators. Indeed, when deemed a real cause, estimated lifetime risks smaller than this (1/100,000) have triggered regulatory evaluation and, sometimes, actual regulation of chemical agents such as airborne benzene. The uncommon, accumulated high-EMF exposures implicated by the evidence about these conditions come from unusual configurations of wiring in walls, grounded plumbing, nearby power lines, and exposure from some jobs in electrical occupations. There are ways to avoid these uncommon accumulated exposures by maintaining a distance from some appliances, changes in home wiring and plumbing, and power lines. However, to put things in perspective, individual decisions about things like buying a house or choosing a jogging route should involve the consideration of well-recognized certain risks, such as those from traffic, fire, flood, and crime, as well as the uncertain comparable risks from EMFs. The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the added personal risk suggested by the epidemiological studies was "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. The three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIEWER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Adult Brain Cancer				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Prone to believe	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

9.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

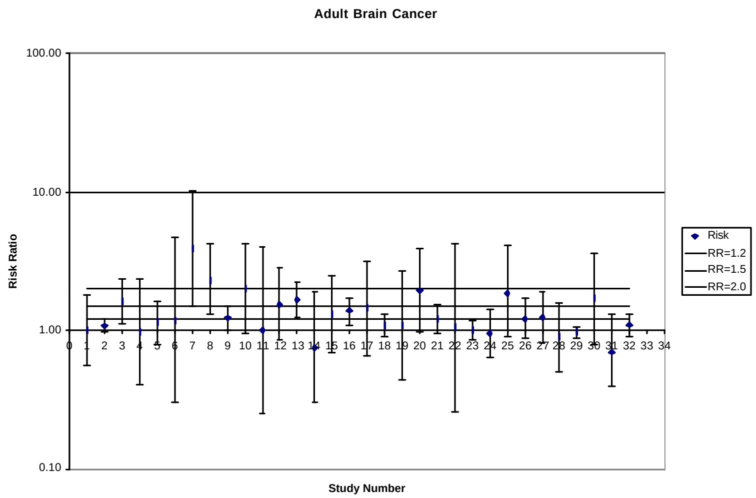

Figure 9.1.1 Studies of Adult Brain Cancer Derived Primarily from Kheifets et al. (1995)

Figure 9.1.1 and Table 9.1.1 summarize the epidemiological evidence for adult brain cancer which is primarily occupational in nature. Of the 29 studies reviewed by Kheifets (Kheifets et al., 1995) in her meta-analysis, 23 had ORs above 1.00 ($p = 0.0004$), and 15 were above 1.2 ($p = 0.14$). The meta-analytic summary of (Kheifets et al., 1995) for the occupational studies was 1.2 (1.1-1.3). If one adds the residential exposure studies of Wrensch, Li, and Feychting (Wrensch et al., 1999), (Li, Theriault & Lin, 1997), (Feychting & Ahlbom, 1994), (Feychting et al., 1997) one sees a similar pattern. The three other studies that focused on Scandinavian electrical railway workers with exposures in the 10 to 100 μT range (Tynes et al., 1994a), (Floderus et al., 1994), and (Alfredsson et al., 1996) did not show high relative risks (see table 9.1.2). On the contrary, RR were close to 1.0 with confidence limits which included a RR of 1.2.

TABLE 9.1.1 KEY FOR FIGURE 9.1.1

Study	No.	Individual Odds Ratio, Mean	Lower CL	Upper CL
(Pearce et al., 1989)	1	1.01	0.56	1.82
(McLaughlin et al., 1987)	2	1.08	0.98	1.20
(Lin et al., 1985)	3	1.62	1.12	2.34
(Vagero et al., 1985)	4	0.98	0.41	2.35
(Tornqvist et al., 1986)	5	1.15	0.80	1.64
(Guberan, 1989)	6	1.18	0.30	4.72
(Speers MA, 1988)	7	3.94	1.52	10.20
(Thomas et al., 1987)	8	2.30	1.30	4.20
(Milham, 1985b)	9	1.23	1.01	1.49
(Coggon et al., 1986)	10	2.00	0.95	4.20
(McMillan, 1983)	11	1.00	0.25	4.00
(Thierault, 1994)	12	1.54	0.85	2.81
(Savitz & Loomis, 1995)	13	1.68	1.26	2.23
(Ryan et al., 1992)	14	0.75	0.30	1.89
(Magnani et al., 1987)	15	1.30	0.70	2.50
(Loomis & Savitz, 1990)	16	1.40	1.10	1.70
(Preston-Martin et al, 1987)	17	1.45	0.66	3.18
(Tynes et al., 1992)	18	1.09	0.91	1.30
(Sahl et al., 1993)	19	1.09	0.44	2.69
(Spinelli, 1991)	20	1.94	0.97	3.88
(Gallagher et al., 1991)	21	1.21	0.95	1.54
(Olin et al., 1985)	22	1.05	0.26	4.20
(Tornqvist et al., 1991)	23	1.00	0.85	1.17
(Juutilainen et al., 1990)	24	0.95	0.63	1.43
(Schlehofer et al., 1990)	25	1.87	0.90	4.10
(Floderus, 1993)	26	1.22	0.88	1.71
(Preston-Martin, 1989)	27	1.25	0.82	1.90
(Demers et al., 1991)	28	0.90	0.50	1.60
(Guenel et al., 1993)	29	0.97	0.89	1.05
(Wrensch et al., 1999)	30	1.70	0.80	3.60
(Feychting & Ahlbom, 1994)	31	0.70	0.40	1.30
(Li et al., 1997)	32	1.10	0.90	1.30

TABLE 9.1.2 MORE DETAILS OF THE STUDIES REVIEWED

INVESTIGATOR, DATE	STUDY POPULATION	METHOD FOR EXPOSURE ESTIMATE	STUDY TYPE	RISK MEASURE	RISK ESTIMATE
(Pearce et al., 1989)	New Zealand: All male cancer patients in Cancer Registry, 1980-1984. 431 cases; 19,904 controls.	Job title	CC	OR	1.01 (0.56-1.82)
(McLaughlin et al., 1987)	Sweden: Cancer Environment Registry, 1961-1979. 3,394 cases.	Occupation and industry codes	Cohort	SIR	1.08 (0.98-1.20)
(Lin et al., 1985)	USa: 951 deaths, 1969-1982.	Usual occupation & industry on death certificate	Mortality	OR	1.62 (1.12-2.34)
(Vagero et al., 1985)	Sweden: Incidence among 2,918 workers at 3 work sites, 1958-1979. 5 CNS cases.	Employment at telecommunication work sites	Cohort	SMR	0.98 (0.41-2.35)
(Tornqvist et al., 1986)	Sweden: Incidence among 10,061 utility workers, 1961-1979. 30 cases CNS cancer.	Job titles	Cohort	SMR	1.15 (0.80-1.64)
(Guberan, 1989)	Switzerland: Incidence among 3,864 workers, 1971-1984. 3 cases.	Job titles	Cohort	SMR	1.18 (0.30-4.72)
(Speers MA, 1988)	US: Male residents, east Texas, 1969-1978. 202 cases; 238 controls.	Usual occupation and industry on death certificate	Mortality	OR	3.94 (1.52-10.2)
(Thomas et al., 1987)	US: White males in Northeast, 1978-1981. 435 cases; 386 controls.	Occupation & industry codes	Mortality	OR	2.30 (1.30-4.20)
(Milham, 1985b)	US: Males working in electrical occupations, 1950-1982. 2,649 Brain cancer deaths, 12,714 controls.	Death certificate occupation	PMR	PMR	1.23 (1.01-1.49)
(Coggon et al., 1986)	England: 2,942 males diagnosed with cancer, 97 CNS cancers as cases, other cancers as controls.	Occupation and industry from postal questionnaire	PMR	PMR	2.00 (0.95-4.20)
(Theriault et al., 1994)	Canada & France: 223,292 electrical utility workers, employed from 1970-1989, 108 brain cancer cases.	Job titles and measurements	CC	OR	1.54 (0.85-2.81)
(Savitz & Loomis, 1995)	US: 138,905 electrical utility workers, employed between 1950-1988. 151 Brain cancer cases.	Job titles and measurements	Cohort	RR	1.68 (1.26-2.23)
(Ryan et al., 1992)	Australia: All incidents of primary brain tumors in adults. 190 brain tumor cases.	Job titles	CC	OR	0.75 (0.30-1.89)
(Magnani et al., 1987)	England: 1,265 males, 1959-1963 and 1965-1979. 423 brain cancer deaths.	Occupation and industrial codes plus job exposure matrix	Mortality	OR	1.30 (0.70-2.50)
(Loomis & Savitz, 1990)	US: All brain cancer deaths in 16 states, 1985-1986.	Job titles	Mortality	OR	1.40 (1.10-1.70)
(Preston-Martin, 1989)	US: Males in L.A. county, 1980-1984. 272 cases.	Job titles with high likelihood of EMF exposure	CC	OR	1.45 (0.66-3.18)

INVESTIGATOR, DATE	STUDY POPULATION	METHOD FOR EXPOSURE ESTIMATE	STUDY TYPE	RISK MEASURE	RISK ESTIMATE
(Tynes et al., 1992)	Norway: 37,945 male workers, 1961-1985. 119 cases brain cancer.	Job title SIR Engine Drivers	Cohort		1.09 (0.91-1.30) 0.67 (0.2-1.6)
(Sahl et al., 1993)	US: 36,221 electrical utility workers, 1960-1988. 32 brain cancer deaths.	Job titles and measurements	Cohort	RR	1.09 (0.44-2.69)
(Spinelli, 1991)	Canada: 4,213 aluminum reduction plant workers, 1954-1985. 8 incidences of brain cancer.	Job activity	Cohort	SIR	1.94 (0.97-3.88)
(Gallagher et al., 1991)	Canada: 320,423 male deaths, 1950-1984. 55 brain cancer deaths.	Job titles	PMR	PMR	1.21 (.95-1.54)
(Olin et al., 1985)	Sweden: 1,254 electrical engineering graduates. 2 brain cancer deaths, 1930-1979.	MS degree in electrical engineering, RIT	Cohort	SMR	1.05 (0.26-4.20)
(Tornqvist et al., 1991)	Sweden: All men working in electrical occupations, 1961-1979. 250 cases of brain tumors.	Job titles	Cohort	SMR	1.00 (0.85-1.17)
(Juutilainen et al., 1990)	Finland: Male industrial workers, 1971-1980. 366 incident brain tumors.	Broad job category	Cohort	RR	0.95 (0.63-1.43)
(Schlehofer et al., 1990)	Germany (Heidelberg region): 1987-1988. 226 incident brain tumors, 418 controls.	Job activities	CC	OR	1.87 (0.90-4.10)
(Floderus, 1993)	Sweden: 1983-1987. 261 brain tumor cases, 1,121 controls.	Job activities and measurements	CC	OR	1.22 (0.88-1.71)
(Preston-Martin, 1989)	US: L.A. county, 1972-1985. 8612 incident brain tumors.	Broad job category	PMR	PIR	1.25 (0.8-1.9)
(Demers et al., 1991)	US: Washington State, 1969-1978. 904 brain cancer deaths	Job titles	Mortality	OR	0.90 (0.5-1.6)
(Guenel et al., 1993)	Denmark: 2.8 persons, 537 brain cancers.	Job titles	Cohort	RR	0.97 (0.9-1.1)
(McMillan, 1983)	2,568 men employed at HM Dockyard Devonport 1955-1975 (UK).	Job activity (Welders)	PMR	PMR	1.00 (0.3-4.0)
(Wrensch et al., 1999)	492 incident gliomas. 462 RDD controls.	Front door spot measures 73 mG	CC	OR	1.7 (0.8-3.6)
(Feychting & Ahlbom, 1994)	223 incident CNS cancer cases. 446 pop. controls.	Historically-estimated residential fields at diagnosis > 2 mG	Nested CC	OR	0.7 (0.4-1.3)
(Feychting et al., 1997)	223 incident CNS cancer cases. 446 pop. controls.	Historical fields > 2 mG occupational JEM > 2 mG	Nested CC	OR Exp both vs. Exp neither	1.3 (0.0-4.8)
(Li et al., 1997)	577 incident brain cancer cases. 552 "other cancer" controls.	Calculated historical magnetic field with field validation > 2mG	CC	OR	1.1 (0.9-1.3)

INVESTIGATOR, DATE	STUDY POPULATION	METHOD FOR EXPOSURE ESTIMATE	STUDY TYPE	RISK MEASURE	RISK ESTIMATE
(Wertheimer & Leeper, 1987)	Death addresses of 1,179 cancer deaths matched with addresses of non-cancer deaths or random sample from city directory of Denver.	Wire code	CC	Ratio of discordant to concordant matched pairs = "Cratio"	C ratio = 227 for "Nerv. System"
(Miller et al., 1996)	24 Malignant (MT) 11 Benign Brain (BT) 2,179 Controls	JEM magnetic and electric fields to job history	Nested CC	OR for > 345 V/m-yrs OR for > 7.1 µT-yrs vs ref.	BT 0.53 MT 0.99 BT0.03-105 MT 2.4 0.5-10.8
(Tynes et al., 1994a)	39 Brain ca, 194 controls from 13,300 electric and non-Norwegian electric train workers.	JEM linked to job history of magnetic and electric fields, control for smoking, creosote, pesticides	Nested CC	OR Reference: 0.1-310 311-3600 µT-yrs	1.0 0.81 (0.3-2.0) 0.94 (0.4-2.3)
(Floderus et al., 1994)	Incident brain cancer (8 engine drivers and 16 conductors) rates compared to general Swedish population, 1961-1969	Job title	Cohort	SIR Engineers Conductors	1.1 (0.6-2.2) 1.3 (0.8-2.1)
(Alfredsson et al., 1996)	Incident astrocytoma (10 engineers, 2 conductors) rates compared to general Swedish population, 1976-1990.	Job title	Cohort	SIR Engineers Conductors	1.0 (0.5-1.8) 0.8 (0.1-3.6)
(Guenel et al., 1996)	69 Incident brain tumors. 276 Controls.	JEM electric fields to job history	Nested CC	OR for > 387 V/m arithmetic mean	3.1 (1.1-8.7)

9.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 9.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the studies are not statistically significant.	(F1) Meta-analysis can help understand the pattern of evidence in epidemiological studies as well as experiments.	(C1) The reviewers think chance alone is an unlikely explanation so that a non-chance explanation including a causal one is relatively more likely.
(A2) Meta-analysis is not appropriate for anything but randomized trials.	(F2) Attending only to statistically significant results avoids false positives, while meta-analysis may avoid false negatives.	
(A3) Chance probably contributes a lot in the apparent pattern of evidence.	(F3) Both the meta-analysis and the sign test on ORs above and below 1.00 suggest that chance alone is not a likely explanation.	
(A4) Many of these studies have multiple comparisons so "p-values" are over-interpreted.	(F4) The later occupational studies had brain cancer and cutpoints pre-specified.	

TABLE 9.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
Residential Studies (A1) Wertheimer's (Wertheimer & Leeper, 1987) study was not blind as to wire code.	(F1) These objections were raised with regard to Wertheimer's childhood studies too, yet the Savitz, London et al., and Feychting studies showed associations with proximity to power lines, even though these studies evaluated incident cases blindly.	(C1) The generic possibility of bias when there is weak experimental and mechanistic support is not a strong argument against causality because bias can affect the risk estimate in either direction.
(A2) Wertheimer's use of deaths might have made the bad survival of poor people and the prevalence of poor people near power lines introduce a bias.	(F2) One should require some evidence for specific bias before pulling down confidence because of bias.	(C2) The universal problem of non-differential exposure misclassification tending to underestimate an effect would lead us to worry about underestimating the effect.
Occupational Studies (A3) Studies with better measurement protocols did not show larger effects, which shows that the exposure misclassification had not been a problem. Our inability to rule out bias should pull down confidence a lot.	(F3) It is not clear how much better these later studies were at reconstructing historic TWAs, much less the reconstruction of other exposure metrics.	(C3) In sum, the issue of bias does not change the reviewers' confidence much; it pulls confidence down a little or not at all.
(A4) Perhaps researchers didn't publish null study associations or results.	(F4) Kheifets (Kheifets et al., 1995) concluded that publication bias was unlikely.	
(A5) There is little or no experimental animal pathology or mechanistic support for a causal interpretation of associations seen, so they must be due to bias or confounding.	(F5) If one has a rule of thumb that all controversial bodies of evidence are by default due to some unspecified bias, one will avoid false positives but also introduce false negatives.	
	(F6) If there is any bias in <u>all</u> these studies, it is downward from non-differential exposure misclassification.	

TABLE 9.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There are not many known risk factors for brain cancer, so one cannot control for them in the analysis.	(F1) By assuming without good experimental and mechanistic support, hidden unknown confounders as a default explanation for results, one avoids false positives but produce false negatives.	(C1) One can never rule out confounding.
(A2) There is little or no experimental animal pathology or mechanistic support for a causal interpretation of associations seen, so they must be due to bias or confounding.	(F2) One should require positive evidence of a confounder to have it pull down confidence.	(C2) However, confounding can affect the risk estimates either way.
	(F3) So far known risk factors such as ionizing radiation have not been associated with EMF exposure or confounded the EMF brain cancer association.	
	(F4) The possibility of unspecified confounding without any supporting evidence should not decrease confidence.	

TABLE 9.2.4

STRENGTH OF ASSOCIATION (*LARGE ENOUGH TO BE CAUSE AND NOT BIAS*?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The association between adult brain cancer and highly exposed jobs and estimated exposures has been estimated meta-analytically as an odds ratio of only 1.2. Many of the individual studies did not reach statistical significance and should have been ignored.	(F1) Occupational and environmental agents may convey a risk which truly is not large enough to be easily detected by epidemiological studies, particularly when they can only estimate historical exposure with surrogate measures. An association, albeit small relative to the resolution power of the body of studies, increases confidence somewhat.	(C1) The effect may be intrinsically weak, so low ORs should not be construed as an argument against causality. An OR slightly above the resolution power of the body studies pulls up confidence in a modest effect of causality somewhat but not as much as a strong association would whose strength would make unidentified bias and confounding less likely.
(A2) This is barely above the resolution power of the combined studies. The absence of a strong association should pull down confidence in a causal explanation for this association a lot because a small association is much more vulnerable to any confounding and bias.	(F2) One needs to invoke one upward bias in all 28 studies of different design and different location or a series of different biases that are only upward. Unknown biases can be downward also.	(C2) The size of the association provides an additional penalty for bias and confounding but not a large one.
(A3) Some of the early, less well-designed studies had higher risk ratios and may have skewed the meta-analysis upward.	(F3) Because of exposure misclassification, the true association may be larger, and therefore less vulnerable to bias than one would think.	

TABLE 9.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One should only consider studies with statistically significant associations.	(F1) Only heeding statistically significant results instead of the overall pattern of evidence, it is true, avoids false-positive results but is a strategy that produces too many false negatives.	(C1) The body of epidemiological evidence on occupational exposures (and to some extent on residential exposures) for adult brain cancer is consistent with an effect just above the resolution power of the various studies.
(A2) The majority of the occupational and residential studies do not show statistically significant results. This is a random pattern of evidence and should pull down the reviewers' degree of certainty a lot.	(F2) Of 29 studies, 23 showed ORs above 1.00 when, by chance, 14 would have been expected. The p-value for 23/29 = 0.0004. The associations are pretty consistently above the null.	(C2) If the effect were statistically significant in all studies (which is tantamount to saying an association that is large relative to the resolution power of the studies), it would have increased confidence a lot.
		(C3) The few residential studies do not alter the confidence. They are consistent with the occupational evidence but do not stand on their own.

TABLE 9.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of these associations are not statistically significant and thus not consistent or homogeneous.	(F1) If EMFs were promoters requiring the presence of initiators whose prevalence varies from place to place, one would expect some inconsistency above and beyond that created by statistical imprecision.	(C1) The various results, occupational and residential, are consistent with an association a little above the resolution power of the studies.
(A2) Kheifets (Kheifets et al., 1995) shows less of an association in Scandinavia and in studies with good designs.	(F2) Perhaps Scandinavia lacks some co-factor. The Scandinavian studies tended to have less exact exposure assessment.	
(A3) Later studies show less of an effect.	(F3) In Kheifets, the average RR of studies fell from 1.29 in 1985 to 1.12 in 1994, only a 13% decrease.	
(A4) The 16/29 better quality studies in Kheifetz show a smaller association. RR =1.06 (1.0-1.12).	(F4) In her meta-analysis of occupational brain cancer studies, Kheifets (Kheifets et al., 1995) found the summary results not sensitive to adding or subtracting individual studies and consistent with a RR of 1.2 (1.1-1.33).	
	(F5) The three "best studies" in Kheifets's meta analysis (Floderus, Theriault, and Savitz) averaged to RR above 1.2 from exposures above the 50th percentile (but showed no monotonic increasing dose response).	

TABLE 9.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Even in occupational studies where cases tended to have higher estimated exposures than did controls, there was not an orderly monotonic increase in relative risk.	(F1) It is true that the presence of an orderly monotonic dose response within and between studies is extremely unlikely by chance or bias and when present would pull up confidence a lot.	(C1) The evidence does not suggest an effect that is large compared to the resolution power of the studies at any dose. Nor does it suggest an effect that becomes ever larger at extremely high occupational exposures. A similar pattern is observed for adult leukemia, where electric train engineers have RRs not much different from utility workers with lower exposures.
(A2) There was no consistent increase in risk estimated by studies investigating occupational groups exposed to levels of 2-5 mG (residence near power lines), 10-20 mG (most heavily exposed electrical occupations), and 70-150 mG (electrical train operators) (see (Floderus et al., 1994), (Tynes et al., 1994a), (Alfredsson et al., 1996), (Tynes et al., 1992)). This lack of dose response should pull confidence down a lot.	(F2) But it is not guaranteed that a suspected promoter acting indirectly on carcinogenisis would always convey linearly increasing risk as dose increased, as is the case with some initiators.	(C2) A promoter or co-promoter truly may not have a monotonically increasing dose response.
	(F3) The effect, if real, is not very large relative to the resolution power of the body of evidence so it would be difficult to discern the shape of a dose response curve in any case.	(C3) Exposure misclassification can mask dose-response relationships (Dosemeci et al., 1990), (DelPizzo, 1992).
	(F4) The approximate methods for reconstructing historical exposures makes this even more difficult.	
	(F5) Using TWA, which may not be the right metric, makes it more difficult still.	
	(F6) The absence of dose response should not pull down confidence much.	
	(F7) Exposure misclassification can mask dose response trends.	

TABLE 9.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Everyone is exposed to electricity, so an epidemic of brain cancer should have been seen as the use of electricity increased.	(F1) There has been an increase in the incidence of brain cancer over the last twenty years.	(C1) To the extent that it suggests anything, the epidemiology suggests that the associations appear in the top percentiles of exposure. An OR of 1.2 applied to the risk of the top 5% of the population would increase the overall rate by a factor of 1.01, not something which would be visible as an epidemic.
		(C2) The increase in brain cancer incidence may be partly due to better diagnosis. Since it is hard to assess how personal EMF exposure has changed in the last 20 years, the reviewers do not think scrutiny of temporal trends in brain cancer is reliable enough to contribute to the confidence of EMF causality.

TABLE 9.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Animal bioassays have shown no increased risk of nervous system tumors.	(F1) Animal bioassays of one aspect of a complex mixture which, if it has any effect, is not linear in risk at high dose, are not highly sensitive. Null results do not pull down confidence as much as positive results should pull them up.	(C1) The animal evidence does not increase confidence but does not pull it down greatly.
	(F2) Experimental studies showing bioeffects at high doses, and isolated studies showing co-promotional effects on other types of cancer should increase confidence somewhat.	

TABLE 9.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no coherent mechanistic chain of events that suggests EMFs as a contributory cause of CNS cancer.	(F1) Many agents do not have mechanistic explanations	(C1) The absence of a mechanistic explanation does not pull down confidence as much as the presence of one would pull it up.

TABLE 9.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See generic discussion.		

TABLE 9.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See generic discussion.		

TABLE 9.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no greater association that is statistically significant with particular cell types.	(F1) Kheifets (Kheifets et al., 1995) mentions a slight tendency for gliomas to show a stronger association.	See "Generic Issues" chapter.

TABLE 9.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 9.2.15

SUMMARY TABLE FOR ADULT BRAIN CANCER			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CONFIDENCE?**
Chance highly unlikely in meta-analysis.	Unlikely		Need non-chance explanation
Upward bias not supported.	Possible	Possible	No impact to slight decrease
Confounding possible but not supported.	More possible	Possible	No impact to slight decrease
Combined effect of chance, bias, confounding.	More possible	Possible	No impact to slight decrease
Strength of association doesn't exceed possible bias or confounding.	More possible	Possible	No impact to slight decrease
Consistency: 23/29 studies have RR = 1.0.	Unlikely	Likely	Increase
Homogeneity: less association in Scandinavian studies but compatible with effect near resolution power of studies.	Possible	Possible	No impact to slight decrease
Coherent with national and temporal trends.	Possible	Possible	No impact
Experimental evidence shows no effect on CNS cancer, but other experimental data suggest bioactivity.	Possible	Possible	No impact to slight decrease
Plausibility: lack of strong mechanistic explanation (chicks, MCF-7).	Possible	Possible	No impact to slight increase
Analogy.	Possible	Possible	No impact
Temporality.	NA	NA	No impact
No specificity of cell type, leukemia association.	Possible	More possible	No impact to slight increase

9.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

9.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

Reviewer 1 (DelPizzo)

Degree of Certainty: The evidence regarding this endpoint has attributes very similar to those of childhood leukemia, with the dose-response relationship being less clear, but the consistency of results being even stronger and the plausibility being increased by having already established a high degree of certainty for the childhood leukemia risk. This reviewer is “prone to believe” that EMFs increase the risk of adult brain cancer to some degree. For the purpose of policy analysis, this reviewer would use values between 60 and 100, with a median of 80 in a certainty scale from 0-100.

IARC classification: “Possible Human Carcinogen, 2B.”

Reviewer 2 (Neutra)

Degree of Certainty: The overall pattern of epidemiological associations is compatible with an effect a little above the resolution power of the body of studies, and the best occupational studies are compatible with a slightly greater effect. The fact that the association is so near the resolution power of the epidemiology leaves it more vulnerable to unspecified bias and confounding, but not so much, with so many studies of different design and location, that one’s confidence is decreased substantially. The lack of obvious animal pathology or mechanistic support pulls confidence down somewhat, but the epidemiological evidence remains and moves one's degree of certainty substantially upward from wherever it started. For the purposes of the policy projects, reviewers need to quantify their degree of certainty and uncertainty. This reviewer is “close to the dividing line between believing and not believing" that EMFs increase the risk of adult brain cancer to some degree. In a certainty scale from 0 to100, he would select 51 and a range form 30 to 70.

IARC Classification: The animal and mechanistic streams of evidence provide little if any support. The epidemiological evidence as usually assessed by IARC would not eliminate all doubts of possible confounding or bias yet it is highly unlikely to be due to chance. In fact, it looks similar to the evidence for adult lymphocytic leukemia except that there is no cell type specificity for adult brain cancer. This warrants a Possible (2B) carcinogen IARC classification, “limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals.”

Reviewer 3 (Lee)

Degree of Certainty: The meta-analysis for the occupational brain cancer studies indicates a slightly higher risk for electrical workers. As a result, this reviewer’s posterior for a relative risk around 1.2 is considerably increased from the initial prior by a consistent association slightly above the resolution power of the many occupational studies and by the positive association of EMF with childhood and adult leukemia. The childhood brain cancer results do not increase the confidence in adult brain cancer. This reviewer’s posterior is only slightly decreased by the fact that for most of the studies, confounding and bias cannot be completely ruled out and by the lack of a dose response. Given the rudimentary way exposure is classified, weak associations such as these are to be expected; a stronger effect may be observed if exposure classification was not as crude. Also, dose-response effects are difficult to detect using such surrogate measures for exposure. The classified groups may not even indicate a gradient of high to low exposure. Hence, this reviewer is “close to the dividing line between believing and not believing' that EMFs increase the risk of adult brain cancer to some degree. For purposes of the policy analysis, she would select 60 with a range of 30 to 75 on a certainty scale ranging from 0 to 100.

IARC Classification: The human evidence is credible but bias and confounding cannot be completely ruled out. The associations observed are weak, however; the strong consistency of slightly positive effects has a very low probability of being explained by chance alone. The animal studies are less than sufficient. There is support from positive findings associated with leukemia. The evidence as a whole is sufficient for a Group 2B classification, “possibly carcinogenic to humans.”

9.3.2 Summary of the Three Reviewers' Classifications

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Adult Brain Cancer				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Prone to believe	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

9.4.1 Questions Relevant to Dose Response and Policy

Table 9.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Guenel (Guenel et al., 1996) found an OR 3.08 (1.08-8.74) for electric field above 387 volt/meter with 12 cases. Miller (Miller et al., 1996) reported an OR of 0.53 (0.03-8.10) for the possibility of an electric field effect. But Guenel and Miller explored the associations between many diseases and many metrics of exposure. Some were bound to come out "significant." (C2) Sahl systematically explored associations with various metrics and found none. (C3) The evidence for or against electric-field effects and brain cancer are not extensive or clear enough to affect confidence. (C4) Floderus (Floderus, 1993) shows slight tendency for "time above 2 mG" to show stronger association than "TWA." The reverse was the case for the leukemias. There is not strong support for one or the other summary exposure metric.	(I1) No consistent guidance possible. Evidence for magnetic field is stronger.

TABLE 9.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The cross-study comparison does not suggest a steady increase in risk over the wide range of human exposure, but the data is insufficient to locate a plateau or threshold, if any. (C2) The evidence is not extensive enough or of such quality to alter one's confidence in the presence or location of thresholds or plateaus.	(I1) No ability to set refined exposure standards.

TABLE 9.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The fact there is an association with (primarily) daytime workshift exposures and perhaps a hint of (primarily) nighttime residential associations would not much support the idea of diurnal differences in vulnerability.	(I1) There is no reason to suspect vulnerable periods.

TABLE 9.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The scant evidence is contradictory. Thieriault et al. (Thierault, 1994) suggest a long latency. (C2) Sahl (Sahl et al., 1993) found no pattern. (C3) Savitz (Savitz & Loomis, 1995) and Guenel (Guenel et al., 1996) suggest shorter incubation periods. (C4) There is weak support for the effect of exposures from the last 5-10 years. This fact makes EMFs more compatible with a promoter than an initiator. One cannot tease out the independent effects, if any, of duration of exposure and interval between first exposure and disease.	(I1) If causal, concern would not be restricted to populations with decades of exposure.

TABLE 9.4.5

EMF COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Except for genetic predisposition, the few suspected risk factors for brain cancer have ORs and attributable fractions which also are not large. Exposure to ionizing radiation, nitrosamines, head trauma, etc. are all rare and have modest associations. They do not account for much of the burden of brain cancer. (C2) The comparison of the size of the EMF "effect" relative to the effect of other agents has no bearing on the confidence in causality or on policy. Cost benefit policy is driven by relative cost per case avoided, not on comparison with other risk factors.	(I1) No impact.

TABLE 9.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A relative risk of 1.2 applied to the low baseline rate of brain cancer over a 40-year occupational period would not exceed 1/1000 lifetime risk but would exceed 1/100,000.	(I1) Might be considered *de minimis* for regulatory purposes for occupational exposure but not for residential exposure.

TABLE 9.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	(I1) No evidentiary base.

TABLE 9.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The later residential studies, which have been viewed as "null," although they are they are compatible with the occupational results, and the later occupational brain cancer studies, are very sophisticated and large, but not large enough. They are some of the best occupational studies done to date. Studies of highly exposed electric train engineers could have been bigger and more detailed. (C2) Any epidemiological study of brain cancer would have the potential problem of confounding by as yet unknown risk factors.	(I1) Larger studies and studies of electric train engineers could be helpful in understanding dose response issues.

TABLE 9.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO MODIFY ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Reanalysis of the Harrington study not likely to cancel evidence to date.	(I1) None

TABLE 9.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Job exposure matrix studies of magnetic and electric fields, contact currents, and shocks using a variety of exposure summary metrics could be used to reanalyze existing data sets related to a variety of diseases and could guide future experimental studies.	(I1) Because brain cancer is a rare and poorly understood disease it may not provide the most relevant policy information.

9.5 CONCLUSIONS ON SCIENTIFICALLY RELEVANT ISSUES

9.5.1 DOSE-RESPONSE ISSUES

The associations reported for neighbors of power lines, exposed vs. unexposed electrical workers, and exposed vs. unexposed electric train workers all are close to the resolution power of the studies. If there is any effect, it does not seem to increase monotonically with dose, although the evidentiary base is insufficient for identifying either thresholds or plateaus of effect. If true, this makes it difficult to assess EMFs in the usual small cancer bioassay which is designed with the assumption that high doses will produce an obvious effect even in a few hundred animals. The evidence on electric fields is limited and contradictory. The possibility that contact currents or repeated shocks might confound magnetic field exposure has been raised for amyotrophic lateral sclerosis (see Chapter 15). There is no evidentiary base to link these other aspects of the EMF mixture to magnetic field exposure. If this were confirmed for ALS it would become a hypothesis for other EMF-associated diseases as well. The evidence for something associated with the TWA magnetic field is compatible with a 1.2-fold relative risk which if true would be of regulatory concern for long-term environmental exposures but might fall below the *de minimis* bench mark of 1/1,000 for occupational exposures.

9.5.2 RESEARCH POLICY

The reviewers are not aware of animal or epidemiological studies in the pipeline that are likely to change the overall assessment. Brain cancer has a number of characteristics that make it difficult to study epidemiologically. It is rare, the causes are poorly understood, and they are not always reliably diagnosed as to histological type. Nonetheless, one or more job exposure matrix studies exploring contact currents, shocks, electric fields, and magnetic fields using various summary exposure metrics would allow one to reanalyze the large occupational cohort and nested case control studies to determine if these other aspects of the EMF mixture might better explain the associations seen with brain cancer and other diseases. From a policy and logistic point of view, brain cancer studies are not the highest priority.